Statistics for the Rest of Us

Interpretation of nonfatal events after cardiac surgery: Actual versus actuarial reporting

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See related editorial on page 207.

Objective: To describe the cumulative incidence (actual) method of analysis and to contrast it with the Kaplan-Meier method.

Method: We use data on porcine valve replacement to illustrate these two statistical techniques.

Results: The "actual" analysis estimates the percentage of events expected to occur. The percentage given by the Kaplan-Meier method is much larger.

Conclusion: Actual (cumulative incidence) analysis is preferred for estimating the probability of occurrence of a nonfatal time-related event.

It is not usually appreciated that the Kaplan-Meier (KM; "actuarial") estimate of event-free percentages, when used for nonfatal time-related events, gives overly pessimistic predictions. Another method, called cumulative incidence analysis, provides the "actual" probabilities of event occurrences.

Survival Curves

Follow-up studies involve the collection of information regarding time-related events, including death and nonfatal events. Instead of the usual summary statistics (eg, mean, standard deviation), a complete description of such time-to-event variables is usually of interest. The proportion of event times that are greater than a given time are plotted as a function of time to produce a survival (or event-free) curve. The result is a curve starting at 100% at time zero and decreasing steadily to 0% at the longest survival time. For a completed series, when all death times are known, the (empirical) survival curve can be readily calculated as the complement of the cumulative sum of deaths at each point in time.

However, in ongoing studies, the investigator cannot know the complete lifetimes of patients who are still alive at the time of the study, and survival curves must be estimated before all of the patients have died. KM analysis solves this problem by assigning to each person who is still alive (called a "censored" observation) a probability of death at each future time equal to the fraction of patients who have already died at that time. This assumes that the distribution of the times to death for currently alive patients will follow the pattern of those who have already died. *Censored* patients are added back into the calculation as future deaths distributed over future time.

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Nonfatal Events

The KM method is also used for events other than death, for example, structural valve deterioration (SVD) or thromboembolism (TE). When applied to an event other than death, this method includes as "censored" any patients who have not yet experienced that event, including those who have died and will never have the event. The resulting event-free estimate attempts to answer the hypothetical question, "What is the risk of the event if no patient ever died?" An alternative method, recently called "actual" analysis in the cardiac literature, modifies this estimate to exclude future events attributed to already deceased patients and answers the more direct question, "What is the risk of the event?"

Example

To illustrate these concepts, we used data from a previous investigation of porcine valve SVD, with 4895 operative survivors of isolated valve replacement and 29,610 valve-years of follow-up.[1] The Gompertz distribution was used to model survival and the Weibull distribution to model SVD. This series contained patients from the beginning of porcine valve usage, using first-generation porcine valves and a mean age of only 60 years. Current results would be expected to be improved, but these suffice for our expository purposes.

Survival (Two-State Model)

A useful technique for describing time-related processes, in this and more complex situations, is the multistate model. For survival analysis, there are 2 states, *alive* and *dead* (Figure 1). All patients begin in the *alive* state and make a transition from *alive* to *dead* at varying times according to some statistical distribution. The transition is inevitable and final: death is called an absorbing state because once a patient reaches that state his process is over. At any point in time, the sum of *alive* plus *dead* is 100% and, at the end of the process, 100% are dead. The survival curve is the plot of the percentage alive over time that corresponds to this process.

SVD (Three-State Model)

As an example of a nonfatal event, we used porcine valve SVD. All valves start in the patient *alive* state, without SVD. In this case, 2 absorbing states exist to terminate the valve's function: it can experience SVD and be explanted, or its host can die before SVD occurs (we ignore SVD that does not result in a terminating event). The horizontal arrows in Figure 2 depict these 2 transitions. We would like to know the probability of the valve ending up in each of those 2 states as a function of time. This is described by 2 curves, which separate all valves into 3 groups at each point in time, corresponding to the 3 states (alive, SVD, and dead) whose total is always 100%. The percentage in the SVD state over time (cumulative incidence) has been called the "actual" probability of SVD.

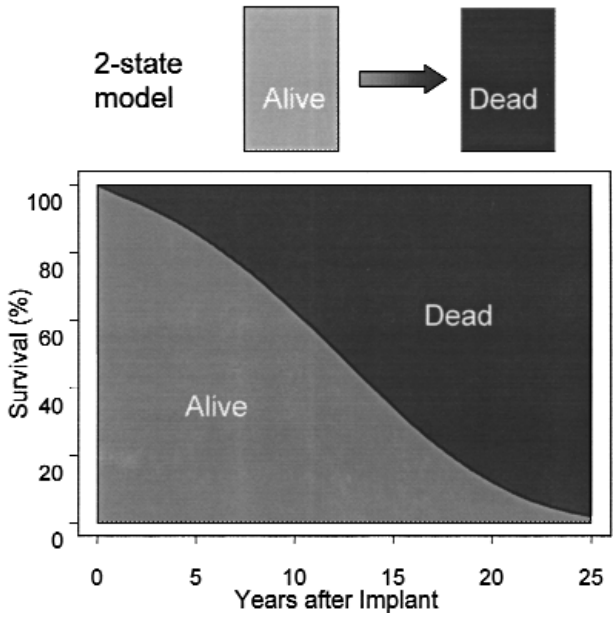

Figure 1. The correspondence between a Kaplan-Meier ("actuarial") survival curve and a 2-state survival process. The process begins with all patients in the alive state at time zero. As patients die, they move from one state to the other according to a time-related process. The percentage alive at each time is plotted by the KM curve. At each time point the alive plus dead patients equal 100%.

The KM method adds another step to this process, as shown by the third (vertical) arrow in Figure 3. It considers that both (1) patients still alive and (2) patients who have died SVD-free are at risk for future SVD; both are "censored" in the computation. This inflates the estimate of SVD and produces a lower SVD-free curve by including the "virtual" occurrences contributed by dead patients. Figure 3 describes the result for the average (60-year-old) patient in this series; for older patients the difference between KM and actual estimates is even greater.

Empirical Validation

We recently provided an empirical validation of the cumulative incidence method using a series of Starr-Edwards valves implanted from 1965 through 1977 and prospectively followed up through 1998, using TE as the nonfatal event.[2] This almost complete series provided an opportunity to compare the KM and actual estimates with the percentage of patients who really had a TE.

For the aortic series, the 30-year KM estimate of TE was 63% and the actual estimate was 34%, with only 33% of the patients having had a TE to date. For the mitral series, the 30-year actuarial and actual TE estimates were 58% and

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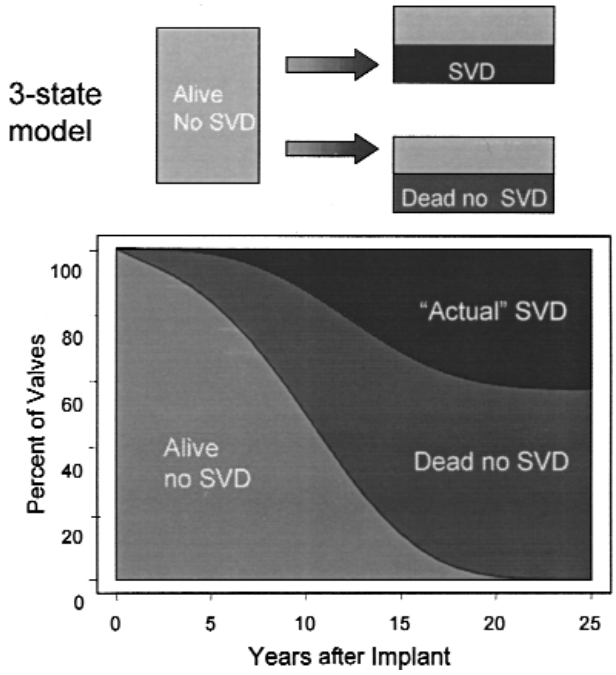

Figure 2. "Actual" analysis of the 3-state process. A valve begins in a functioning state in a living patient and can end its experience in one of two ways. The valve can fail (SVD) before the patient dies, or the patient can die before SVD happens. Both states (SVD and dead) are terminating states; once a valve enters them it cannot leave and the process is over. At each time point the sum of alive plus SVD plus dead equals 100%. The cumulative incidence of SVD over time is called "actual" SVD.

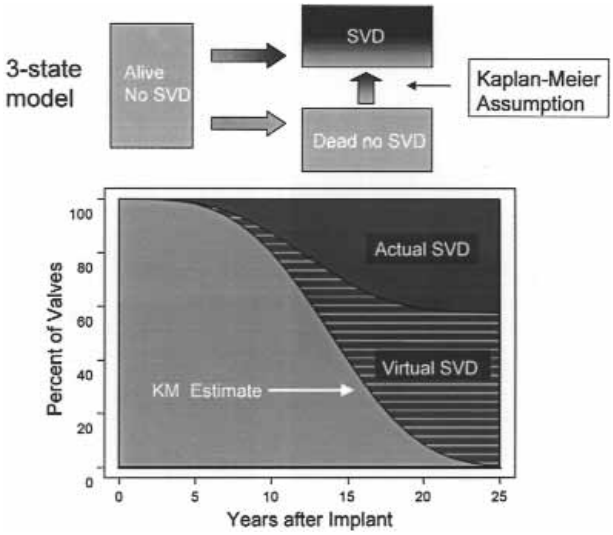

Figure 3. "Actuarial" or KM analysis of the 3-state process. This is the same process as in Figure 2. The KM estimate uses an additional assumption, that the patients who died before SVD will eventually have SVD. The consequence of this is to add additional SVD valves, shown here as "virtual" SVD.

42%, respectively, and 41% had had a TE. Thus, in both positions, the actual estimates were much lower than the KM estimates and only slightly higher than the percentage of patients who had had a TE to date. Only a few additional TEs would be expected to occur before 30 years, because only a few patients remained at risk.

Conclusion

For event-free analysis, the cumulative incidence (actual) method, unlike the KM method, assumes that only living patients continue to be at risk for a future event and thus estimates the events actually sustained. The result is that the actual event percentages are smaller than the KM estimates, and more so in older patients.

The actual method provides a valid probability of failure and is essential for individual patient counseling and population management. For example, for management of patients with failure-prone implanted cardiac devices, it is the actual estimate of failure that must be weighed against the risk of prophylactic explantation.

Appendix: A Note on Terminology

Actuarial analysis originally referred to the life-table method, where events are grouped into intervals.[3] Since the availability of computers, the KM method[4] is used almost universally. It is called the product-limit method because it can be considered a life-table method in which the intervals are so small that they contain only one event time. In this sense, it could be considered part of the actuarial family. The essence of the 2 methods is the same—incorporating partially completed lifetimes by the technique of censoring. In the case of survival, the censoring refers to patients still alive. In the case of nonfatal events, censoring is done for patients still free of the event, including deaths.

Actual analysis is a relatively new designation. Many terms have been used in the statistical literature. Cumulative incidence is generally preferred,[5,6] but several other adjectives have been used as well, including *crude*,[7] *unadjusted*,[8] *absolute*,[9] *influenced*,[10] and *observable*.[11] Recently the term *actual* was used to refer to the cumulative incidence method,[12] and this term seems to be accepted in the cardiac literature.[13-18]

Acknowledgment

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